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(54) Title: A NOVEL AMORPHOUS FORM OF [2-[4-[(4-CHLOROPHENYL)-PHENYL METHYL]-1- PIPERAZINYL] ETHOXY] ACETIC ACID DIHYDROCHLORIDE (CETIRIZINE DIHYDROCHLORIDE)

(57) Abstract: The present invention relates to a novel amorphous form of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride suitable for pharmaceutical formulations and process for the preparation thereof.

FORM-2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION
(SECTION 10)

A Novel Amorphous Form of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] Acetic Acid Dihydrochloride (CETIRIZINE DIHYDROCHLORIDE)

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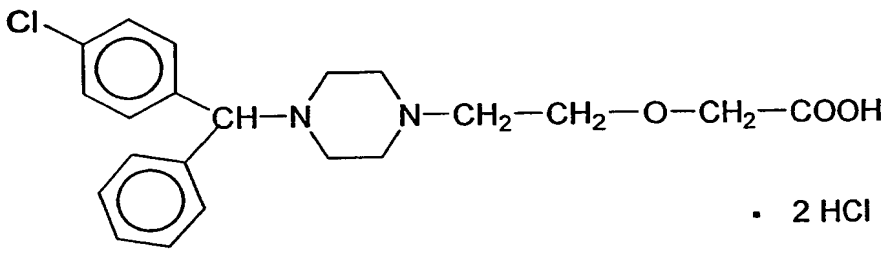
The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed.

FIELD OF THE INVENTION

The present invention relates to a novel amorphous form of [2-[4-[(4-chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid dihydrochloride, which is generically known as Cetirizine dihydrochloride and marketed under brand name 'Zyrtec'® in U.S. markets.

The present invention also relates to processes for the preparation of a novel amorphous form of Cetirizine dihydrochloride, which can be depicted as Formula (I).



Formula (I)

BACKGROUND OF THE INVENTION

Cetirizine is used for the treatment of allergic syndromes such as chronic and acute allergic rhinitis, allergic conjunctivitis, pruritus, urticaria and etc. The product was proven to be remarkably free from side effects on the central nervous system.

USP 4,525,358 claims Cetirizine and its pharmacologically acceptable salts, which includes dihydrochloride and the process for the prepration was disclosed in the experimental section. A process for the preparation of cetirizine dihydrochloride

comprises hydrolysis of the methyl ester of Cetirizine using ethanolic potassium hydroxide solution, followed by the reaction workup to afford the potassium salt of cetirizine. The potassium salt of cetirizine was acidified with hydrochloric acid to get the Cetirizine base and accompanied by the formation of dihydrochloride salt in toluene.

USP 6, 255, 487 disclosed a process for the preparation of Cetirizine dihydrochloride, which comprises the condensation of (4-chloro phenyl) phenyl methyl chloride and potassium 2-(1-piperazinyl) ethoxyacetate in acetonitrile and followed by the reaction workup to get the Cetirizine base accompanied by formation of the dihydrochloride salt in acetone media using concentrated hydrochloric acid.

WO 01/29016 disclosed the process for the preparation of Cetirizine dihydrochloride, which comprises condensation of 1[(4-chlorophenyl) phenyl methyl] piperazine with tertiary butyl 2-(2-chloroethoxy) acetate in dimethylformamide in presence of sodium carbonate to get the tertiary butyl ester of Cetirizine which was further hydrolysed with hydrochloric acid to result the Cetirizine base and formation of dihydrochloride salt in acetone media using concentrated hydrochloric acid.

WO 00/52000 disclosed a process for the preparation of Cetirizine dihydrochloride, which comprises hydrolysis of diethyl acetal of Cetirizine with aq.hydrochloric acid to give the relevant aldehyde. The obtained aldehyde was oxidized with hydrogen peroxide in alcohol and followed by the reaction workup to afford the Cetirizine base. The dihydrochloride salt was prepared in acetone media using concentrated hydrochloric acid.

Although, many of the related patents disclosed processes for the preparation of Cetirizine and its salts including dihydrochloride through various synthetic methods, none of these patents describe the solid state thereof such as an amorphous form of Cetirizine or its dihydrochloride.

It has been disclosed earlier that amorphous forms of a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to crystalline forms [Konne T., Chem. Pharm. Bull. 38, 2003 (1990)]. For some therapeutic indications one bioavailability pattern may be favoured over another. An amorphous form of Cefuroxime axetil is a good example for exhibiting higher bioavailability than the crystalline form.

During our laboratory experimentation as a part of process development, a novel amorphous form of Cetirizine dihydrochloride was unexpectedly discovered during crystallization of the pharmaceutically acceptable salts of Cetirizine in different solvents.

Hence, one aspect of the present invention is to provide a novel amorphous form of Cetirizine dihydrochloride.

Another aspect of the present invention is to provide processes for the preparation of the novel amorphous form of Cetirizine dihydrochloride. The novel amorphous form of cetirizine dihydrochloride was characterized by X-ray powder diffractogram, which is not having well-resolved peaks.

The processes of the present invention are simple, eco-friendly and easily scalable.

SUMMARY OF INVENTION

The present invention relates to a novel amorphous of Cetirizine dihydrochloride.

The present invention also relates to processes for the preparation of the novel amorphous of Cetirizine dihydrochloride. One embodiment of the processes for the preparation of amorphous form of cetrizine dihydrochloride comprises dissolution of Cetirizine in aqueous mixture of water miscible or immiscible solvent using hydrochloric acid and further isolation by adding water immiscible aromatic or cyclic or acyclic aliphatic hydrocarbon solvent or ethers.

BRIEF DESCRIPTION OF THE ACCOMPANYING DRAWINGS

Fig-1 is a diagram showing the X-ray powder diffraction of amorphous form of Cetirizine dihydrochloride.

DETAILED DESCRIPTION OF THE INVENTION

One embodiment of the present invention provides a novel amorphous form of Cetirizine dihydrochloride. Another embodiment of the present invention provides a process for preparing a novel amorphous of Cetirizine dihydrochloride. It is to be noted that the term, Cetirizine is used to encompass all [2-[4-[(4-chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid regardless of its optical properties and thus to include its each enantiomer individually or mixture thereof.

The amorphous form of Cetirizine dihydrochloride of the present invention was characterized by X-ray powder diffractogram, which was measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The X-ray powder diffraction pattern of the amorphous form of Cetirizine dihydrochloride has no well-resolved peaks, which indicates the formation of an amorphous form.

The novel amorphous form of [2-[4-[(4-chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride (Cetirizine dihydrochloride) of the present invention can be prepared by a process, which comprises,

a. dissolving Cetirizine in an aqueous mixture of water miscible solvent(s) like C_1-C_5 straight or branched chain alcoholic solvents such as methanol, ethanol, n-propanol, isopropanol, 2-butanol, n-butanol, n-pentanol or 2-pentanol, preferably isopropanol or ketone solvents such as acetone, methyl ethyl ketone or 2-pentanone preferably acetone or nitrile solvents such as acetonitrile or propionitrile, preferably acetonitrile or water immiscible aromatic or cyclic or acyclic aliphatic hydro carbon solvent such as toluene, xylene, cyclohexane or heptane, preferably toluene using hydrochloric acid;

b. filtering the reaction solution;

c. distilling off the solvent from reaction solution under vacuum at a temperature of 30-100^{O}C;

d. isolating the solid by optionally adding a non-polar solvent including aromatic or cyclic or acyclic aliphatic hydrocarbon solvent such as toluene, xylene, cyclohexane or heptane, preferably cyclohexane or ethers such as diethyl ether, di isopropyl ether, diisobutyl ether, preferably diisopropyl ether;

e. drying the compound at a temperature of 40-120^{O}C to afford the desired amorphous form of Cetirizine dihydrochloride.

The amorphous form of cetirizine dihydrochloride is prepared in an alternate route using non-amorphous Cetirizine dihydrochloride, which comprises;

a) dissolving non-amorphous form of Cetirizine dihydrochloride in an aqueous mixture of water miscible solvent(s) like C_1-C_5 straight or branched chain alcoholic solvents such as methanol, ethanol, n-propanol, isopropanol, 2-butanol, n-butanol, n-pentanol or 2-pentanol, preferably isopropanol or ketone solvents such as acetone, methyl ethyl ketone or 2-pentanone preferably acetone or nitrile solvents such as acetonitrile or propionitrile, preferably acetonitrile or water immiscible aromatic or cyclic or acyclic aliphatic hydro carbon solvent such as toluene, xylene, cyclohexane or heptane, preferably toluene;

b) filtering the reaction solution;

c) distilling off the solvent from reaction solution under vacuum at a temperature of 30-100^{O}C;

d) isolating the solid by optionally a non-polar solvent including aromatic or cyclic or acyclic aliphatic hydrocarbon solvent such as toluene, xylene, cyclohexane or heptane, preferably cyclohexane or ethers such as diethyl ether, di isopropyl ether, diisobutyl ether, preferably diisopropyl ether;

e) drying the compound at a temperature of 40-120^{O}C to afford the desired amorphous form of Cetirizine dihydrochloride.

The ratio of weight of cetirizine or its dihydrochloride to volume of hydrochloric acid may be varied from 1: 0.5 to 2, preferably 1:0.6, and the ratio of weight of cetirizine or its dihydrochloride to volume of water is from 1:1 to 10, preferably 1:5. Similarly, the ratio of weight of cetirizine or its dihydrochloride to volume of solvent is from 1:1 to 15, preferably 1:10.

The amorphous form of the present inventive substance may have moisture content varying from 0.3 to 12.0% by KF method but preferably have the moisture content of around 1.8 to 5.6% by KF method. The moisture content of present inventive substance was measured on Mettler DL-35 instrument using Karl-Fischer reagent.

The amorphous form of the present inventive substance is thermally stable, and hence it may be well suited for pharmaceutical formulations. Furthermore, the processes for the preparation of present invention are simple, eco-friendly and commercially viable.

The present invention is illustrated by the following examples, which are not intended to limit the effective scope of the claims.

Reference Example:

Preparation of Cetirizine:

[2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetamide (50 grams) in 6.5%w/v aqueous sodium hydroxide (200 ml) was refluxed till the reaction was substantially completed. Then the reaction mixture was cooled, further diluted with water (300 ml) accompanied by adjusting the pH of the reaction solution around 9.0 with concentrated hydrochloric acid and the resulted reaction mass was washed

with ethyl acetate. The pH of the separated aqueous layer was further adjusted to 4.0 with concentrated hydrochloric acid and the product was extracted with dichloromethane. Then the combined dichloromethane layer was evaporated under vacuum to get the required Cetirizine base. (43.0 grams).

Preparation of a novel amorphous Form of Cetirizine dihydrochloride:

Example 1:

Cetirizine (5.0 grams) was taken in a mixture of acetone (50 ml) and water (25 ml), and concentrated hydrochloric acid solution (5.0 ml) was added into the mixture, which was stirred to get a clear solution. Then, the reaction solution was filtered and distilled off the solvent completely to dryness at a temperature of 80-90^{O}C under vacuum. Cyclohexane (50 ml) was added to the residual mass and stirred for 30 minutes at a temperature of 30-35^{O}C. The obtained compound was filtered, washed with cyclohexane (25 ml) and on subsequent drying at a temperature of 60-65^{O}C to a constant weight resulted the novel amorphous form of Cetirizine dihydrochloride. (Weight: 4.8 grams; M.C by KF: 3.9%)

Example 2:

Cetirizine (5.0 grams) was taken in a mixture of toluene (50 ml) and water (25 ml), and concentrated hydrochloric acid solution (5.0 ml) was added the mixture, which was stirred to get a clear solution. Then, the reaction solution was filtered and distilled off the solvent completely to dryness at a temperature of 80-90^{O}C under vacuum. Toluene (50 ml) was added to the residual mass and stirred for 30 minutes at a temperature of 30-35^{O}C. The obtained compound was filtered, washed with toluene (25

ml) and subsequently dried at a temperature of 60-65°C to a constant weight resulted the novel amorphous form of Cetirizine dihydrochloride.

(Weight: 4.8 grams, M.C by KF: 6.4%)

Example -3:

Cetirizine (5.0 grams) was taken in a mixture of acetonitrile (50 ml) and water (25 ml), and concentrated hydrochloric acid solution (3.0 ml) was added into the mixture, which was stirred to get the clear solution. Then, the reaction solution was filtered and distilled off the solvent completely to dryness at a temperature of 70-80°C under vacuum to result the amorphous form of cetirizine dihydrochloride.

(Weight: 6.1 grams; M.C by KF: 4.4%)

Example-4:

Cetirizine dihydrochloride (25.0 grams) was dissolved in water (100 ml) and further stirred at a temperature of 25-35°C to get a clear solution. Acetone (300 ml) was added to this solution and stirred for 15-30 minutes. The solvent was distilled off from the reaction solution completely to dryness at a temperature of 80-85°C under reduced pressure to result the amorphous form of cetirizine dihydrochloride. The amorphous form of cetirizine dihydrochloride was further dried at a temperature of 100-125°C for 4-5 hours (Weight: 24.0 grams; M.C by KF: 2.4%).

The sample was kept aside at ambient conditions for about 15 days and analyzed for moisture content, which was enhanced to 4.7%.

Example-5:

Cetirizine dihydrochloride (5.0 grams) was dissolved in water (15 ml) at a temperature of 25-35°C. Toluene (50 ml) was added to the reaction solution and

distilled off the solvent completely to dryness from the reaction solution at a temperature of 75-80^{O}C. Then cyclohexane (100 ml) was added to the residual mass and stirred for 45-60 minutes at a temperature of 25-35^{O}C to crystallize the solid mass. The separated solid was filtered, washed with cyclohexane (25 ml) and subsequently dried at the temperature of 60-70^{O}C to a constant-weight amorphous form of Cetirizine dihydrochloride (Weight: 4.8 grams; M.C by KF 5.9%).

Example-6:

Cetirizine dihydrochloride (50.0 grams) was dissolved in a mixture of water (200 ml) and acetone (500 ml), further stirred to get a clear reaction solution at a temperature of 25-35^{O}C. Filtered the reaction solution and distilled off the solvent completely under vacuum, Then cyclohexane (250 ml) was added and stirred the reaction mixture at 25-35 ° C for 30 to 40 minutes to crystallize the solid mass. The separated solid was filtered and washed with cyclohexane (100.0 ml) and on subsequent drying at the temperature of 60-110^{O}C to a constant-weight the amorphous form of Cetirizine dihydrochloride (Weight: 49.8 grams; M.C by KF 2.92%).

A sample from the above compound was kept under humidity conditions for 24 hours and analyzed for moisture content, which was enhanced to 10.0%.

Example-7:

Cetirizine dihydrochloride (5.0 grams) was dissolved in water (15 ml) at a temperature of 25-35^{O}C. Isopropanol (50 ml) was added to the reaction solution and distilled off the solvent completely to dryness from the reaction solution at a temperature of 75-80^{O}C. Then di isopropyl ether (100 ml) was added to the residual mass and stirred for 45-60 minutes at a temperature of 25-35^{O}C to crystallize the solid

mass. The separated solid was filtered, washed with di isopropyl ether (25 ml) and subsequently dried at a temperature of 60-70^{O}C to a constant-weight the novel amorphous form of Cetirizine dihydrochloride (Weight: 5.0 grams; M.C by KF 6.2%).

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWING

Fig.1 is characteristic X-ray powder diffraction pattern of novel amorphous form of Cetirizine dihydrochloride.

The XRD pattern of the compound obtained from the above examples are similar, which are not having well resolved peaks. Vertical axis: Intensity (CPS); Horizontal axis: 2 Theta (degrees). It shows a plain halo with no peaks, which is characteristic of the amorphous nature of product.

We claim:

1. A novel amorphous form of [2-[4-[(4-chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride (Cetirizine dihydrochloride).
2. The novel amorphous form of claim 1 being characterized as amorphous by Powder X-ray diffractogram.
3. The amorphous form according to claim 2, having an X-ray powder diffraction pattern substantially in accordance with Figure (1).
4. The amorphous form of Cetirizine dihydrochloride of claim 1 having moisture content varying from 0.3 to 12.0% by KF method.
5. The amorphous form of Cetirizine dihydrochloride of claim 4, wherein said moisture content is from 1.8 to 5.6% by KF method.
6. A process for the preparation of a novel amorphous form of [2-[4-[(4-chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid dihydrochloride (Cetirizine dihydrochloride), which comprises,

a) dissolving Cetirizine in a mixture of water and one or more organic solvents with an assistance of hydrochloric acid;

b) filtering the reaction solution;

c) removing the solvent from the reaction solution;

d) isolating the solid by optionally adding a non-polar solvents; and

e) drying the compound at a temperature of 40-120^{O}C to afford the desired amorphous form of Cetirizine dihydrochloride.

7. The process of claim 6, wherein said organic solvent is a water miscible solvent selected from the group consisting of C_1-C_5 straight or branched aliphatic alcohol including methanol, ethanol, n-propanol, isopropanol, 2-butanol, n-butanol, n-pentanol or 2-pentanol; ketone solvents including acetone, methyl ethyl ketone or 2-pentanone; or nitrile solvents including acetonitrile or propionitrile.
8. The process of claim 7, wherein said water miscible solvent is isopropanol.
9. The process of claim 7, wherein said water miscible solvent is acetone.
10. The process of claim 7, wherein said water miscible solvent is acetonitrile.
11. The process of claim 6, wherein said organic solvent is a water immiscible solvent selected from the group consisting of toluene, xylene, cyclohexane or heptane.
12. The process of claim 11, wherein said water immiscible solvent is toluene.
13. The process of claim 6, wherein said non-polar solvent is selected from the group of toluene, xylene, cyclohexane, heptane, ethers including diethyl ether, diisopropyl ether, diisobutyl ether or mixtures thereof.
14. A process for the preparation of novel amorphous form of [2-[4-[(4-chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid dihydrochloride (Cetirizine dihydrochloride), which comprises,
    a) dissolving non-amorphous form of Cetirizine dihydrochloride in a mixture of water and one or more organic solvents;
    b) filtering the reaction solution;
    c) removing the solvent from the reaction solution ;

d) isolating the solid by optionally adding a non-polar solvent; and

e) drying the compound at a temperature of 40-120^{O}C to afford the desired amorphous form of Cetirizine dihydrochloride.

15. The process of claim 14, wherein said organic solvent is a water miscible solvent selected from the group consisting of C_1-C_5 straight or branched aliphatic alcohol including methanol, ethanol, n-propanol, isopropanol, 2-butanol, n-butanol, n-pentanol or 2-pentanol; ketone solvents including acetone, methyl ethyl ketone or 2-pentanone; or nitrile solvents including acetonitrile or propionitrile.

16. The process of claim 15, wherein said water miscible solvent is isopropanol.

17. The process of claim 15, wherein said water miscible solvent is acetone.

18. The process of claim 15, wherein said water miscible solvent is acetonitrile.

19. The process of claim 14, wherein said organic solvent is a water immiscible solvent selected from the group consisting of toluene, xylene, cyclohexane or heptane.

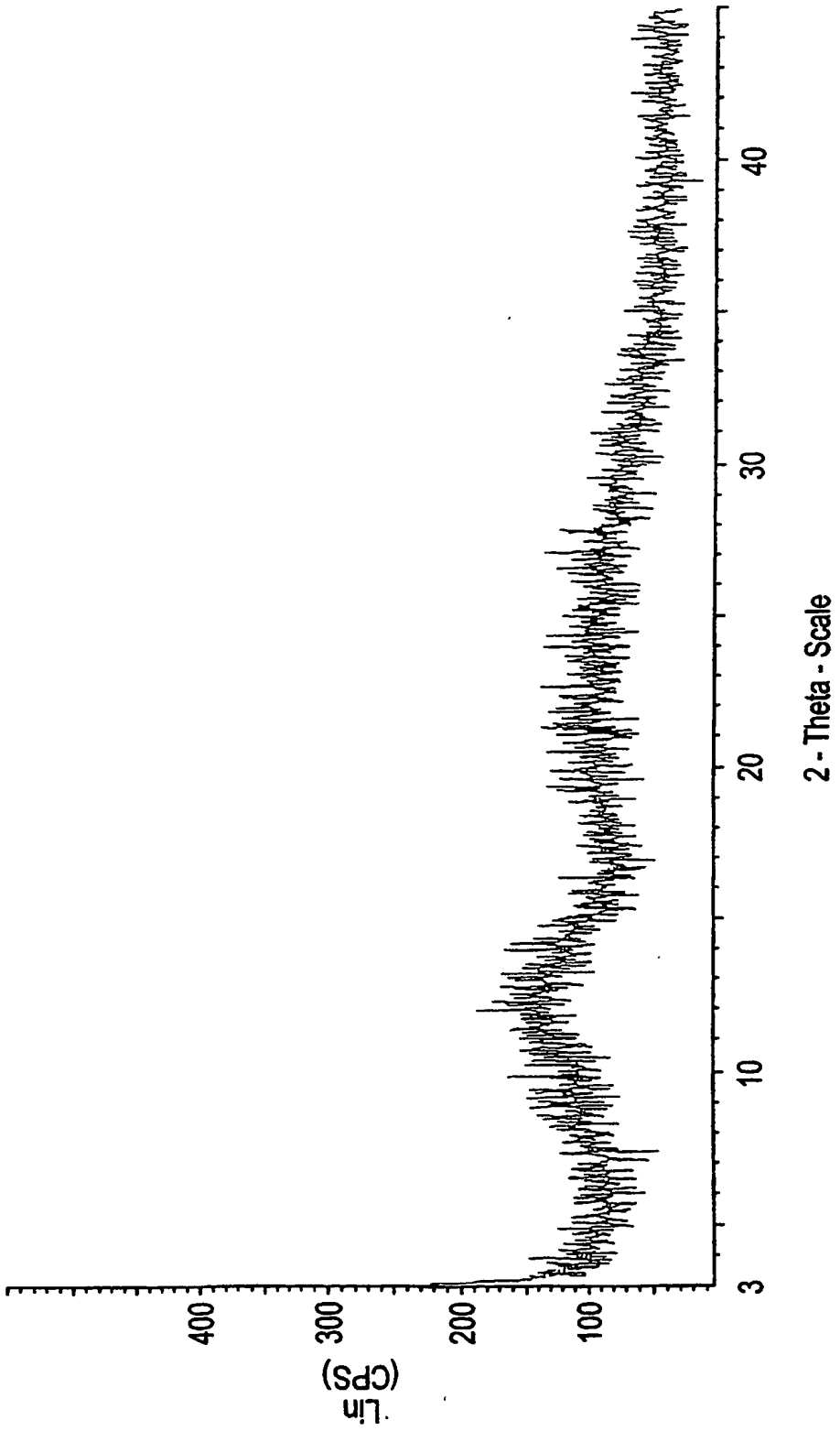
20. The process of claim 19, wherein said water immiscible solvent is toluene.

21. The process of claim 14, wherein said non-polar solvent is selected from the group of toluene, xylene, cyclohexane, heptane, ethers including diethyl ether, diisopropyl ether, diisobutyl ether or mixtures thereof.

22. An amorphous form of [2-[4-[(4-chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride (Cetirizine dihydrochloride) prepared according to the process of claim 6.

23. An amorphous form of [2-[4-[(4-chlorophenyl)-phenyl methyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride (Cetirizine dihydrochloride) prepared according to the process of claim 14.

FIG. 1



INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/US 03/17600

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 52000 A (TREPPENDAHL SVEND PETER ;FISCHER ERIK (DK); GEA FARMACEUTISK FABRI) 8 September 2000 (2000-09-08) cited in the application example 1C	1-23
A	US 6 239 277 B1 (HERNANDEZ PEDRO E ET AL) 29 May 2001 (2001-05-29) cited in the application example 2	1-23

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
10 September 2003	30/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Von Daacke, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern[illegible] Application No
PCT/US 03/17600

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	OPALKA C J ET AL: "A NOVEL SYNTHESIS OF THE ENANTIOMERS OF AN ANTIHISTAMINE DRUG BY PIPERAZINE FORMATION FROM A PRIMARY AMINE" SYNTHESIS, GEORG THIEME VERLAG. STUTTGART, DE, vol. 7, no. 7, July 1995 (1995-07), pages 766-768, XP000979124 ISSN: 0039-7881 * page 767, right column at the end: workup procedure *	1-23
A	EP 1 120 109 A (PFIZER PROD INC) 1 August 2001 (2001-08-01) page 6, line 21,22; claim 23; example 1; table 2	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern I Application No
PCT/US 03/17600

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